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T CELLS

Selection and tolerance involve autophagy

Although the process of T-cell selection in the thymus has been described in detail, little is known about the pathways of antigen presentation that are used by thymic epithelial cells (TECs) to present self-antigen-derived epitopes for the positive and negative selection of thymocytes. Now, Klein and colleagues show that autophagy in TECs has a role in shaping the T-cell repertoire and is essential for the induction of central tolerance.

Autophagy, a process that targets damaged organelles for degradation through the fusion of autophagosomes with lysosomes, has recently been shown to generate peptides that are presented by MHC class II molecules. Autophagy-related gene 5 (*Atg5*) has an essential role in autophagosome formation, such that loss of this gene results in a block in autophagy. TECs, unlike many other cells, have a high level of constitutive autophagy, which suggests that this process might have a role in delivering self antigens for presentation.

To examine the role of autophagy in T-cell selection, the authors transplanted *Atg5*$^{-/-}$ embryonic thymi under the renal capsule of a panel of T-cell receptor (TCR) transgenic mice. Indeed, interfering with autophagy in TECs led to altered selection of certain MHC class II-restricted TCRs, but did not affect selection of MHC class I-restricted TCRs. The authors also showed that the abundance of a particular peptide–MHC class II complex (I-Eα_{52-68}–I-A^{b}), which is usually under-represented in cortical TECs (cTECs), was increased in cTECs in the absence of autophagy, indicating that autophagy influences the composition of MHC class II ligands in cTECs. So, the authors suggest that autophagy in cTECs has a role in the positive selection of MHC class II-restricted T cells by generating specific epitopes for MHC class II-mediated presentation by cTECs.

Medullary TECs (mTECs) have a non-redundant role in the induction of tolerance through the promiscuous expression of tissue-restricted self antigens, so the authors next examined the role of autophagy in tolerance. *Atg5*$^{+/+}$ or *Atg5*$^{-/-}$ thymi were grafted under the renal capsule of athymic mice. Mice that received *Atg5*$^{-/-}$ thymi developed a severe wasting disease, with inflammatory infiltrates in the colon, liver, lung, uterus and Harderian gland. By contrast, mice that received *Atg5*$^{+/+}$ thymi did not show any signs of autoimmunity, suggesting that impaired presentation of tissue-restricted antigens by mTECs in the thymus, owing to a defect in autophagy, might allow for the escape of autoreactive T cells into the periphery. Future work is required to dissect the mechanistic aspects of this failure of self tolerance, for example, to determine whether negative selection and/or the induction of regulatory T cells is affected.

Taken together, the data indicate that autophagy in TECs shapes the selection of the T-cell repertoire in the thymus and is essential for the induction of central tolerance.

Olive Leavy

ORIGINAL RESEARCH PAPER Nedjic, J. *et al.* Autophagy in thymic epithelium shapes the T-cell repertoire and is essential for tolerance. *Nature* 13 August 2008 (doi:10.1038/nature07208)
FURTHER READING Vyas, J. M., Van der Veen, A. G. & Ploegh, H. L. The known unknowns of antigen processing and presentation. *Nature Rev. Immunol.* **8**, 607–618 (2008)